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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

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21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/448,946	SINGH, ARJUN	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 1996 and 24 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-64* is/are pending in the application.

4a) Of the above claim(s) *61-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *22 July 1996* is: a)☐ approved b)☒ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In response to the Supplemental Amendment filed 2/4/03, prosecution of the instant application is hereby resumed. The amendment filed 7/22/96 has been entered. Claims 1, 6, 9-17, 24-25 were cancelled. Claims 2-5, 7, 8, 18, 19, 22 and 23 were amended, and claims 26-46 were added. Subsequently, the amendment filed 2/4/03 has been entered. Claims 2-5, 7, 8, 18-23, and 26-46 were cancelled, claims 47-64 were added, and are now pending. No arguments have been provided in the amendment of 2/24/03.

Applicant's arguments in the amendment filed 7/22/96 are directed to claims subsequently cancelled by the amendment of 2/24/03. These arguments are largely moot and have not been considered beyond the extent they apply to the pending claims. Consequently, should Applicant attempt to re-introduce the claims presented in the 7/22/96 amendment in response to the final rejection, they will not be entered as such an amendment would require new search and consideration.

The obviousness-type double-patenting rejection over application 07/552,719 is withdrawn due to the abandonment of the application following an adverse decision by the Federal Circuit, *Singh v. Brake*, 65 USPQ2d 1641 (CA FC 2003).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 61-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11, filed 7/22/96.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

The preliminary amendment filed with the instant application amended page 1, lines 21-23 to indicate that applications 07/552,719; 06/506,098; 06/501,352; and 06/488,323 were incorporated by reference. The amendment also indicates that the instant application is a continuation of the '719 application. However, neither the '719 nor the '098 application had incorporated the disclosure of any parent application by reference. Consequently, the instant application as amended contains new subject matter, and is therefore a continuation-in-part of the '719 application, not a continuation. The first sentence of the specification should be amended to indicate the proper relationship to the '719 application.

However, should Applicant wish to maintain the relationship between the instant application and the '719 application as a continuation, the phrase "which applications are

incorporated herein by reference" should be deleted from the first line of the specification, as amended. See also notification of defective declaration *infra*.

> This application is claiming the benefit of a prior filed nonprovisional application under 35 U.S.C. 120, 121, or 365(c). Copendency between the current application and the prior application is required.

The instant application claims priority to 06/501,352, filed 6/6/83 through 06/506,098, filed 6/20/83. However, the '352 application was incompletely filed, which was never corrected, and thus it was never pending, i.e. it was abandoned as of its filing date. Consequently, the '352 and '098 applications were not copending. Reference to the '352 application should be removed from the first line of the specification, as amended.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required along with the surcharge under 37 CFR 1.16(e). See MPEP §§ 602.01, 602.02 and 602.05(a).

> The oath or declaration is defective because:
> The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 601.01(a).

As indicated above the instant application as filed (and amended) is a continuation-in-part of the '719 application due to the preliminary amendment filed with the instant application. Consequently, the copy of the declaration filed with the '098 application does not adequately identify the instant application. See MPEP 602.05(a).

However, should Applicant choose to delete the phrase "which applications are incorporated herein by reference" from the first line of the specification, as amended, then a new

oath or declaration would not be required, i.e. the original declaration would be proper, since the instant application would then truly be a continuation of the '719 application.

Drawings

The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on 7/22/96 have been disapproved because they introduce new matter into the drawings. 37 CFR 1.121(f) states that no amendment may introduce new matter into the disclosure of an application. The original disclosure does not support the proposed Figures 13, 14, 15A, 15B, 16, and 17 for the reasons set forth below under the objection to the specification under 35 USC 132. These figures accompany new matter added to the specification, filed 7/22/96.

In order to avoid abandonment, the drawing informalities noted in Paper No. 4, mailed on 1/18/96, must now be corrected. Correction can only be effected in the manner set forth in the above noted paper. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The requirement for corrected drawings will not be held in abeyance.

Specification

The amendment filed 7/22/96 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the text inserted at page 1, line 27, and at page 8, line 32; page

21, line 31; page 22, lines 9, 11, 12, and 13; and page 32, line 23; and proposed Figures 13, 14, 15A, 15B, 16, and 17.

The text inserted at page 1, line 27, adds information concerning application 07/541,186, being filed as a continuation of application 06/488,337. As a result of the amendment, the '186 application is incorporated by reference. However, the original specification did not mention the '186 application, much less incorporate it by reference. Consequently, the inserted material is new matter, and the phrase "which was filed as a continuation having Serial No. 07/541,186 filed June 20, 1990, now issued as U.S. Pat. No. 5,101,003," should be deleted.

The text inserted at page 8, line 32; page 21, line 31; page 22, lines 9, 11, 12, and 13; and page 32, line 23 and proposed Figures 13, 14, 15A, 15B, 16, and 17 are text and figures excerpted from applications 06/438,128 and 06/452,227, which are mentioned in passing on pages 21 and 22 of the original specification. Applicant argues (page 27 of amendment filed 7/22/96) that the original specification incorporated these applications by reference. However, the original specification contains no language that indicates either the '128 or '227 applications were incorporated by reference, much less that the specific material being added to the instant specification was to be incorporated by reference. In order for the inserted material to have been properly incorporated into the original specification by reference, the original specification would have had to indicate that the material from these applications was incorporated by reference, identify with detailed particularity what specific material was being incorporated from the applications, and identify where in each application the material was to be found. See MPEP 609.01(p) and *In re Lund and Godtfredsen*, 153 USPQ 625, 631 (CCPA 1967); *In re De Seversky*, 177 USPQ 144, 146-147 (CCPA 1973); and *Advanced Display Systems Inc. v. Kent*

State University, 54 USPQ2d 1673, 1679 (CA FC 2000). The original specification fails to do any of these. Consequently, the inserted material was not incorporated by reference and is neither part of nor supported by the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

The disclosure is objected to because of the following informalities:

The application as amended on 7/22/96 contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §§ 1.821(a)(1) and (a)(2). However, this application now fails to comply with the requirements of 37 C.F.R. §§ 1.821 through 1.825. The instant application was filed as a continuation of an application filed before 37 C.F.R. §§ 1.821 through 1.825 went into effect, and contained no new sequences. Consequently, the instant application was exempt form compliance with these rules. However, the amendment of 7/22/96 includes new nucleotide and/or amino acid sequences not present in the parent application. Consequently, the instant application is no longer exempt and must now fully comply with 37 C.F.R. §§ 1.821 through 1.825.

Applicant must supply a computer readable form (CRF) copy of the "Sequence Listing", a paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. Any response to this Office Action which fails to meet all of these requirements

will be considered non-responsive, unless Applicant chooses to delete the newly added sequences as indicated below. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits.

Appropriate correction is required.

As set forth in the objection to the specification under 35 USC 132, substantial material, which contains the newly added sequences, inserted into the specification by the amendment filed 7/22/96 is new matter. Should Applicant choose to delete the new matter as directed in the preceding objection, the objection for informalities would also be obviated, i.e. the application would again be exempt from compliance with 37 C.F.R. §§ 1.821 through 1.825.

Claim Rejections - 35 USC § 112

Claims 55-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to claims 55-57 as directed to yeast expression vectors comprising DNA encoding bovine interferon or rennin, the specification fails to provide an adequate description of how the expression vehicles comprising a gene bovine interferon and rennin were constructed. Construction of vehicles comprising genes for bovine interferon and rennin are described on pages 21-22, however the description refers to plasmids disclosed in patent applications as the source of the DNA; this information was not available to the public at the time the invention was made. No DNA sequence information has been provided in the specification for these genes nor the identity of the expression vectors pertaining thereto.

Applicant's arguments filed 7/22/96 have been fully considered but they are not persuasive. With respect to the arguments concerning IGF-I or IGF-II, the claims do not embrace this subject matter. Consequently, the arguments are moot and were considered no further. With respect to bovine interferon and rennin, the material added to the specification by amendment is new matter, see objection to the specification *supra*. The requirements of 35 USC 112, first para., must be met at the time the application is filed. The requirements cannot be met by later supplementing the disclosure with new material not originally disclosed therein. No additional arguments were provided in the amendment of 2/24/03.

Claims 55-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for yeast expression vectors comprising DNA encoding human interferon alpha 1, does not reasonably provide enablement for yeast expression vectors comprising DNA encoding bovine interferon, tissue plasminogen activator or rennin. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The written description of the construction of expression vehicles comprising DNA encoding bovine interferon and rennin, is inadequate because the plasmid source of the DNA was not adequately described, i.e. available to the public, and no nucleotide sequence for these genes was provided. Also, no expression vehicle has been identified that contains these genes.

With respect to the gene for tissue plasminogen activator, the application discloses plasmid p68, comprising DNA encoding tissue plasminogen activator, that is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, i.e. expression of tissue plasminogen activator, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or

statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Since no accessible source of a cloned DNA or its nucleotide sequence has been provided for the bovine interferon or rennin, and it is not clear that the plasmid source of the tissue plasminogen activator gene, i.e. the prior art cited, was available to the public, the skilled artisan would be required to first clone these genes in order to practice the inventions claimed. No guidance or citation of relevant prior art has been provided that would enable the skilled artisan to isolate the necessary genes. In the absence of such information the skilled artisan would be required to engage in excessive experimentation involving inventive activity in order to clone and characterize the insulin-like growth factor gene in order to construct the expression vehicle claimed or use the expression vehicle to produce the protein by the claimed methods. Such experimentation would be undue.

Applicant's arguments filed 7/22/96 have been fully considered but they are not persuasive. While claims 9 and 24 have been cancelled, new claims 55-57 are directed to the subject matter of claim 9. No arguments were provided in the amendment of 2/24/03.

Claims 48-51, 53, 54, 56, 57, 59 and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression vehicle comprising DNA encoding the first 85 amino acids of yeast alpha mating factor pre-sequence ending with arginine operably connected in translation reading frame to DNA encoding the mature human interferon alpha 1, does not reasonably provide enablement for other yeast alpha mating factor prepro sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification is unclear on what constitutes the pre-sequence, the pro-sequence or the pre-pro peptide of the mating factor pre-pro polypeptide (page 9, lines 14-17). In view of the examples, it has been assumed that the pre-sequence and pre-pro peptide corresponds to an N-terminal peptide of alpha factor with a carboxy terminus ending with Lys-Arg or a Glu-Ala dipeptide. The "protein" recited in the claims that is secreted or recovered has been assumed to be mature protein since the only protein recited in the claims is encoded by DNA that encodes a "mature protein". Claims drawn to expression vehicles and yeast organisms transformed with the expression vehicles are included in this rejection as the specification teaches only using these products for the production of the heterologous proteins encoded by the expression vehicles "in discrete form unaccompanied by any substantial peptide presequence or other artifact of expression, as a product of yeast expression, processing and secretion" (see specification, page 6, lines 6-22).

The specification teaches at page 2, lines 10-17 that at the time the invention was made that secreted proteins have evolved with signal sequences that are well suited for secretion of that

particular protein through a cell membrane. At page 4, lines 25-27, it is taught that the secretory processes in yeast were not fully understood. It is also stated at page 16, lines 15-17 that the processing steps for yeast precursor proteins are unpredictably different from those of mammalian precursor proteins.

The specification provides only a single working example of a yeast transformed with an expression vehicle which produces a mature heterologous protein, at pages 25-27, wherein the protein is initially expressed as a fusion with an N-terminus pre-sequence of the first 85 amino acids ending with Arg of yeast alpha mating factor pre-pro protein fused to the mature interferon polypeptide. The specification discloses yeast that can secrete other heterologous proteins that are initially expressed as a fusion with an 89 amino acid pre-sequence having two Glu-Ala repeats. However, as disclosed on page 20, no "mature" human interferon alpha 1 was produced as the species produced retained both Glu-Ala repeats, and on page 25, only 24% of the bovine interferon produced was processed was "mature", with the major species retaining both Glu-Ala repeats. It is noted that the "mature" protein in these two cases comprised N-terminal amino acids not present in the native mature proteins, being an artifact of the construction of the fusion gene. It is not clear from these results whether fusion proteins lacking these additional amino acids would be properly processed and secreted. Of the remaining examples described by Table I, only trace amounts of renin and tissue plasminogen activator were secreted and the secreted proteins were not analyzed with respect to complete or proper processing. However based on the results with the two interferon species, one of skill would expect that the other proteins would also be incompletely processed. Furthermore, in the amendment filed 7/22/96 (pages 37-40),

Applicant explains the necessity of using only the prepro sequence up to the first Lys-Arg, i.e. the first 85 amino acids.

Szebo et al. (1986) discloses that 95% of a consensus interferon expressed as a pre-pro-alpha-factor fusion protein with or without Glu-Ala repeats at the processing site was retained in the cell (page 5859, col. 2 para. 1; Fig. 3, page 5860). Of the secreted protein, the majority of the protein secreted from the construct having the repeats was properly processed, while 50% of the protein produced from the construct lacking the repeats was unprocessed, i.e. not cleaved at Lys-Arg (page 5860). Zsebo et al. disclose in contrast to their findings, work by others indicated that gene fusions containing the Glu-Ala repeats resulted in the secretion of heterologous proteins with incompletely processed N-termini (page 5860, col. 2).

The specification teaches generally that at the time the invention was made, the secretory process of yeast was not well understood. The results disclosed in the specification and by Zsebo et al., well after the time the invention was made, indicate that secretion of "mature" protein using an alpha factor pre-sequence was unpredictable. Since the specification provides only a single working example of a yeast capable of secreting a mature heterologous protein, the breadth of the claim is not commensurate in scope with the enabling disclosure. It would therefore require undue experimentation for one skilled in the art to practice the invention as claimed in order to modify the vectors to ensure proper processing of any heterologous protein fused to alpha factor pre-sequences.

Applicant's arguments filed 7/22/96 have been fully considered but they are not persuasive. Applicant's arguments pertain to claims 2-4, 7-8, 16, 18-19, and 22-23, and the limitations recited therein, as allegedly overcoming the grounds of rejection. However, these

claims have been cancelled by the amendment filed 2/24/03, and replaced with claims that do not recite the limitations discussed. No arguments have been provided in the amendment of 2/24/03.

Claim Rejections - 35 USC § 102 & 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Claims 47-60 are rejected under 35 U.S.C. 102(e) & (g) as being clearly anticipated by Brake et al., US 4,870,008.

See claims 1-37 and para. bridging col. 6-7 disclosing that the "Gene*" may be an interferon or rennin. Also see *Singh v. Brake,* 55 USPQ2d 1673 (CA FC 2000) and 65 USPQ2d 1641 (CA FC 2003). The instant claims embrace the subject matter claimed in Brake and the count in the interference decided by the Court between Brake and 07/552,719, which is a parent of the instant application. The interference was decided in favor of Brake.

Claims 47-54 and 58-60 are rejected under 35 U.S.C. § 102(e) as being anticipated by Kurjan et al. (U.S. 4,546,082).

The claims are drawn to yeast expression vehicles comprising DNA encoding heterologous proteins, which can be a mature protein, operably connected to the yeast alpha

factor promoter and/or in translation reading frame to DNA encoding the pre-pro peptide of yeast alpha factor, yeast organisms transformed with such vectors, and methods of producing heterologous proteins or mature heterologous proteins from cultures containing such cells or more specifically from the media as secreted protein.

Kurjan et al. disclose yeast expression vehicles comprising a fusion of a segment of the yeast alpha factor gene, encoding the first 89 amino acids of the precursor protein, and DNA encoding mature heterologous proteins, such that a fusion protein is produced and secreted from cells containing such vehicles, followed by isolation of the protein from the media (Abstract; Fig. 1, 3-5; col. 5, lines 20-36, col. 10-12). It is presumed that the alpha factor promoter was present on the vector used since the 1.7 kb EcoRI fragment (R1-2) containing the alpha factor gene was sufficient to direct expression of alpha factor (Table 2, col. 8).

Claims 47-54 and 58-60 are rejected under 35 U.S.C. § 102(e) as being anticipated by Brake et al. (U.S. 4,914,026). The claims are drawn to yeast expression vehicles comprising DNA encoding heterologous proteins, which can be a mature protein, operably connected to the yeast alpha factor promoter and/or in translation reading frame to DNA encoding the pre-pro peptide of yeast alpha factor, yeast organisms transformed with such vectors, and methods of producing heterologous proteins or mature heterologous proteins from cultures containing such cells or from the media as secreted protein.

Brake et al. disclose an expression vehicle for the production of "mature" proinsulin, i.e. processed to remove alpha factor sequences, secreted into the culture media which comprise DNA encoding proinsulin fused in translation reading frame at its N-terminus with a segment of

the alpha factor gene comprising its promoter and the pre-pro polypeptide (up to the HindIII site)(col. 6, lines 42-59), yeast cells containing the expression vehicle, and methods of producing and isolating the secreted protein (col. 3, line 9 to 40; col. 4, line 56 to col. 5, line 9; col. 8, lines 10-57).

Claims 55-57 are rejected under 35 U.S.C. § 103 as being unpatentable over Kurjan et al. (U.S. 4,546,082) as applied to claims 47-54 and 58-60 above, and further in view of Goeddel et al. (U.S. 4,762,791).

The claims are drawn to yeast expression vehicles comprising DNA encoding mature human interferon operably connected to the yeast alpha factor promoter and/or in translation reading frame to DNA encoding the pre-pro peptide of yeast alpha factor, yeast organisms transformed with such vectors, and methods of producing and isolating human interferon from cultures containing such cells or more specifically from the media as secreted protein.

Kurjan et al. (U.S. 4,546,082) disclose yeast expression vehicles comprising a fusion of a 5' segment of the yeast alpha factor gene, encoding the first 89 amino acids of the precursor protein, and DNA encoding mature heterologous proteins, such that a fusion protein is produced and secreted from cells containing such vehicles, followed by isolation of the protein from the media (Abstract; Fig. 1, 3-5; col. 5, lines 20-36, col. 10-12). It is presumed that the alpha factor promoter was present on the vector used since the 1.7 kb EcoRI fragment (R1-2) containing the alpha factor gene was sufficient to direct expression of alpha factor (Table 2, col. 8). Kurjan et al. suggest fusing the coding information for useful proteins, such as interferon, to the N-terminal segment of the alpha-factor gene for secretion of the protein lacking superfluous amino acids from the yeast into the media (col. 3, lines 10-17). The reference also teaches that industrial production of mammalian proteins from yeast may have advantages over production from bacteria since the presence of mammalian proteins may have an adverse effect on bacterial cell

metabolism and the yeast secretion and processing system is known to be similar to other eukaryotes (col. 2, lines 31-45). The reference does not teach either a source of interferon DNA or the DNA sequence.

Goeddel et al. teach the cloning and nucleotide sequence of pre- and mature human interferon gamma (Fig. 4-5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the DNA encoding the mature interferon gamma as taught by Goeddel et al. in the expression system of Kurjan et al. with a reasonable expectation of success. One would have been motivated to do so because of the explicit teaching by Kurjan et al. that interferon could be produced by their expression system.

Applicant's arguments filed 7/22/96 have been fully considered but they are not persuasive. Applicant's arguments are directed to claims cancelled by the amendment filed 2/24/03. To the extent Applicant's argument that the references fail to show certain features of applicant's invention apply to the pending claims, it is noted that the features upon which applicant relies (i.e., absence of Glu-Ala-Glu-Ala from the prepro sequence) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

The new ground(s) of rejection presented in this Office action were either necessitated by Applicants amendment or prompted by the submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 1/29/96. Accordingly, **THIS**

ACTION IS MADE FINAL. See MPEP § 609(B)(2)(i) and 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Scott D. Priebe
Primary Examiner
Art Unit 1632